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(54) Title: METAL IMPLANTS

(57) Abstract: A metal implant for use in a surgical procedure is provided with a surface layer that is integral with the metal sub-
strate, and which incorporates a biocidal material. The surface layer is grown by anodising at a voltage between 50 and 150 V, and
the biocidal material incorporated in it by ion exchange. This produces a significantly harder surface than anodising at low voltage,
and generates pits containing ion-absorbing material.

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Metal Implants

This invention relates to metal implants for use in surgical procedures, and in particular to the
5 introduction of a biocidal material into such implants to suppress or control infection.

Various surgical procedures require the use of implants. For example cancerous bone may be removed, in
10 prosthetic surgery, to be replaced by a metal implant. Such an implant may for example be of titanium alloy, which is very strong and relatively light. To ensure a hard-wearing surface the provision of a titanium nitride coating has been suggested. There is furthermore a risk
15 of introducing infection when implanting such metal implants, and it has been suggested that metallic silver might be electroplated onto metal implants, the silver being a biocidal material that can control infection without causing toxic effects to the patient. However
20 such coatings, whether of titanium nitride or silver, may be undercut due to corrosion from body fluids, so that the coating may detach from the implant, which may increase wear and cause tissue damage. WO 03/089023 describes a way of pretreating an implant by anodising at
25 10 V to form a phosphate layer, and then incorporating biocidal silver ions in this layer by ion exchange. A way of making a significantly improved layer has now been found.

30 According to the present invention there is provided a method of treating a titanium metal implant for use in a surgical procedure, so as to form a surface layer that is integral with the metal substrate and which incorporates a biocidal material, wherein the method
35 comprises anodising the implant at a voltage above 50 V for a period of at least 30 min, so as to generate a

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surface layer, and then performing ion exchange so as to incorporate ions of a biocidal metal into the surface layer.

5 The biocidal material should preferably be effective for at least 6 weeks, preferably for up to 6 months after surgery, and the release rate should be low to avoid toxic effects on body cells. Furthermore the total quantity of biocidal material is preferably also limited
10 to minimize any toxic effects. Performing the anodising at a voltage above 50 V has two effects: it initially generates a dense hard surface layer whose thickness is primarily determined by the voltage, and it then generates shallow pits in the surface which are filled
15 with a somewhat softer and more porous material. The absorption of biocidal metal ions is primarily into the material within the shallow pits, so that the total quantity of biocidal material and its release rate can be controlled by controlling the magnitude of the anodising
20 voltage and its duration, so as to control the number and size of the shallow pits. The anodizing might be carried out at a voltage as high as 500 V or 750 V, but more usually is performed between 50 V and 150 V. The duration may be up to 24 hours, but preferably no more than 12
25 hours, for example 2 hours or 6 hours.

It is also desirable if the surface is highly polished before production of the surface layer. This may for example be achieved by electropolishing. One
30 benefit of performing the anodising at a voltage in this significantly higher range is that the surface finish is not deleteriously affected; if the surface is polished before anodising so as to be shiny, then it will remain shiny after the high-voltage anodising step. This is in
35 contrast to the effect of low voltage anodising, which generates a milky or matt appearance at the surface.

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In principle, a range of different materials may be used for the biocidal material. Gold, platinum and palladium would be potentially suitable, although expensive; silver is preferable as it is not particularly
5 soluble in body fluids due to the presence of chloride ions and the low solubility of silver chloride. Other elements such as copper, tin, antimony, lead, bismuth and zinc might be used as ions combined into the surface layer. The rate of release would be controlled, in this
10 case, primarily by the strength of the absorption of the metal ions in the layer.

The term titanium metal implant refers to an implant of a metal that is predominantly titanium, preferably at
15 least 75% titanium by weight. The invention is applicable to prosthetic implants that are made of pure titanium, or a titanium alloy. The standard alloy for this purpose is titanium 90% with 6% aluminium and 4% vanadium (British standard 7252).

20

Preferably the implant is initially polished to provide a very smooth surface. Titanium alloy can be electro-polished using acetic acid, or a mixture of nitric and hydrofluoric acids. Alternatively the implants
25 might be subjected to a combination of anodic passivation with mechanical polishing, which may be referred to as electrolinishing, this process removing the oxide that protects surface roughness, the surface at that point then being electrochemically re-passivated, so producing
30 a mirror-smooth finish. Various electrolytes are suitable for this purpose, including nitric acid mixed

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with sulphuric acid, sodium hydroxide, sodium phosphate, or sodium hydroxide mixed with sodium nitrate.

After polishing the surface of the metal, surface
5 conversion can take place. A layer of metal oxide or phosphate is formed by anodising in a suitable electrolyte, so that the oxide or phosphate layer builds up at the surface of the metal, as described above. Biocidal metal ions can then be absorbed from an aqueous
10 salt solution into the oxide or phosphate matrix, for example the ions Ag^+ or Cu^{++} . Cations of palladium, platinum or even ruthenium could be absorbed in a similar way. If desired, deposited silver, platinum or palladium could then be converted to metal within the oxide or
15 phosphate surface coating, this reduction being performed chemically or electrochemically or by light.

The invention will now be further and more particularly described, by way of example only, and with
20 reference to the accompanying drawings in which:

Figure 1 shows a diagrammatic sectional view through part of the surface of an implant subjected to a low voltage anodising treatment;
25

Figure 2 shows a corresponding sectional view of an implant subjected to a high-voltage anodising treatment of the invention; and

30 Figure 3 shows the surface composition profile of a specimen treated as in figure 2, the profile being determined by secondary neutral mass spectrometry.

A hip implant is made of titanium alloy (Ti/Al/V).
35 The implant is cleaned ultrasonically using first acetone as the liquid phase, and then a 1 M aqueous solution of

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sodium hydroxide, and is then rinsed in de-ionised water. The surface is initially shiny, with a pale grey colour. The cleaned implant is then immersed in a stirred 12% (weight) solution of phosphoric acid, and is anodised for 5 2 hours at a maximum voltage of 100 V and a maximum current of 10 mA/cm², so as to form a surface coating of titanium oxide and phosphate. Within a couple of minutes a dense dielectric layer is formed on the surface, and the current then adopts a stable low value for the rest 10 of the anodising period. The surface forms a hard surface layer which can have different coloured appearances due to optical interference effects; during the initial stage of anodising, the surface colour varies from purple/blue, through blue, green, yellow, orange, and then finally 15 red. Anodising at 100 V produces a film thickness of about 0.14 µm (140 nm). The anodised implant is then rinsed in de-ionised water again.

The implant is then immersed in a stirred 0.1 M 20 aqueous solution of silver nitrate, and left for 2 hours. As a result of ion exchange there is consequently some silver phosphate in the titanium phosphate coating. The implant is then ready to be implanted. During exposure to body fluids there will be a slow leaching of silver 25 ions from the phosphate layer, so that any bacteria in the immediate vicinity of the implant are killed. Infection arising from the implant is therefore suppressed.

30 Referring to figure 1, where anodising of a titanium implant 30 is performed at 10 V for 2 hours, the current falls to a low value over the first couple of minutes during anodising, but the current then rises again with the formation of a porous surface layer with 20 µm 35 macropores and 1 µm micropores. This produces a porous high-surface-area layer 32 which is about 2 µm thick, of

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hydrous titanium oxide and phosphate. This is highly effective at absorbing silver ions, and can provide an initial silver capacity of about 70-100 $\mu\text{g}/\text{cm}^2$; this is well below the toxic level, but more than adequate to
5 provide a biocidal effect.

Referring to figure 2, where anodising is performed at a high voltage such as 100 V for 2 hours, as mentioned above the current initially falls to a low value, and
10 then remains steady. The surface forms a hard anodised oxide layer 34 typically of thickness about 0.14 μm , but in which there are pits 36 typically of diameter about 5 μm and depth about 0.4 μm which are filled with titanium oxide as a result of hydrolysis from localised titanium
15 dissolution. Such pits 36 are approximately circular in plan, and make up between 15 and 20% of the surface area. Surface analysis techniques have confirmed that, after ion exchange treatment, the absorbed silver is associated with the titanium oxide/phosphate phase at the surface;
20 this is true for both the low voltage and the high-voltage anodising procedures. The high-voltage anodised surface absorbs silver to a small extent at the outer surface of the hard layer 34, and to a larger extent within the more porous material in the pits 36; overall
25 there is somewhat less initial capacity for silver, typically about 9 $\mu\text{g}/\text{cm}^2$. This is still sufficient to provide the required biocidal effect.

Thus the effects of anodising at 100 V for 2 hours
30 are to produce a hard and compact oxide layer whose thickness depends upon the voltage (the relationship being approximately 1.4 nm per volt) this film having a coloured appearance determined by the film thickness, and retaining the surface microstructure (e.g. polished
35 finish). Furthermore the surface is pitted, with pits about 0.3 μm deep filled with hydrous titanium dioxide

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covering slightly less than a fifth of the surface. This can be loaded with silver at about $9 \mu\text{g}/\text{cm}^2$.

Measurements of the surface composition at different
5 depths below the surface have been measured using
secondary neutral mass spectrometry on a titanium alloy
specimen treated as described above. The results are
shown in figure 3, to which reference is now made. It
will be observed that in the surface region, down to
10 about $0.14 \mu\text{m}$ (marked by the broken line), the
composition is about 73% oxygen and about 18% titanium,
with phosphorus at about 6%; this corresponds to the hard
surface layer 34. There is then a zone in which the
titanium concentration increases and the oxygen
15 concentration decreases, down to about $0.4 \mu\text{m}$; this
corresponds to the depths at which there are pits 36
containing titanium oxide. At greater depths the
composition is evidently a titanium/aluminium alloy.

20 Measurements have also been made of the loss of
silver from the surface of the anodised implant into a
brine flowing over the surface (at a linear velocity of
about $0.7 \text{ ml cm}^{-2} \text{ h}^{-1}$). The initial rate of silver release
over the first 24 hours is about $0.1 \mu\text{g cm}^{-2} \text{ h}^{-1}$, the
25 release rate then gradually falling over the next 24
hours to about half that value, then remaining steady for
another 48 hours, before decreasing again. But
throughout this period the concentration of silver in the
leaching brine was sufficient to be biocidal.

30 The silver capacity can be adjusted in three ways.
It may be changed by changing the number of pits, and
this can be either by changing the voltage, or by
changing the concentration of pitting agents (such as
35 chloride or fluoride ions) which are present as
impurities in the phosphate electrolyte. For example the

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concentration of such monovalent ions can be decreased by a selective anion exchange treatment; or their concentration could be increased by adding appropriate acids. For example the concentration of chloride ions might be increased by adding NaCl or hydrochloric acid to the phosphoric acid electrolyte, preferably such that the chloride ion concentration is no more than 500 ppm, more preferably no more than 50 ppm. Alternatively the pits might be grown to larger depths and diameters; this may be achieved by carrying out the anodising for a longer period of time.

It may also be appropriate to change the current density.

15

By anodising at a higher voltage the thickness of the hard oxide layer can be increased, for example being about 0.7 μm at 500 V. Once this layer has been formed, as indicated by the decrease in the current, the voltage might be changed. During this second stage the pits are formed, and gradually grow in size, and this may be carried out at a lower voltage.

It will be appreciated that the invention is also applicable to implants which are at least partly made of porous titanium, as the high-voltage anodising process is effective within the pores. This can lead to significantly higher loading of silver per unit volume of implant, because of the much larger surface area.

30

The electrical connection to the implant, so that anodising can be performed, may for example be through a titanium wire spot-welded onto the implant. Alternatively a blind hole may be drilled into the implant, and electrical connection made by a screw connector in this hole, a sealant (for example silicone)

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preventing electrolyte access to the contact area.
Exposed parts of the connector can be protected from
anodisation for example by a PTFE insulating tape. After
the anodising process, the connector would be removed,
5 and the hole could be filled by a bio-compatible plug,
for example of anodised titanium, or of a polymer.

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Claims

1. A method of treating a titanium metal implant for use
in a surgical procedure, so as to form a surface layer
5 that is integral with the metal substrate and which
incorporates a biocidal material, wherein the method
comprises anodising the implant at a voltage above 50 V
for a period of at least 30 min, so as to generate a
surface layer, and then performing ion exchange so as to
10 incorporate ions of a biocidal metal into the surface
layer.
2. A method as claimed in claim 1 wherein the anodising
is performed so as to generate a dense hard surface layer
15 and also shallow pits in the surface which are filled
with a somewhat softer and more porous material, and
wherein the magnitude of the anodising voltage and its
duration are controlled, so as to control the number and
size of the shallow pits.
- 20 3. A method as claimed in claim 1 or claim 2 wherein the
the biocidal metal is silver.
4. A method as claimed in any one of the preceding
25 claims wherein the anodising step uses an electrolyte
comprising phosphoric acid.
5. A method as claimed in claim 4 wherein the phosphoric
acid is of concentration between 5% and 20% by weight.
- 30 6. A method as claimed in claim 4 or claim 5 wherein the
electrolyte comprises chloride ions at a concentration no
more than 500 ppm.

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Fig.1.
(Prior art)

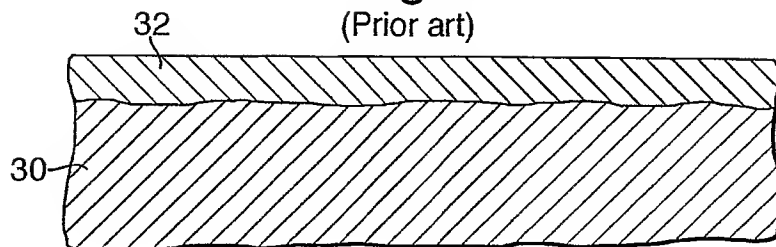


Fig.2.

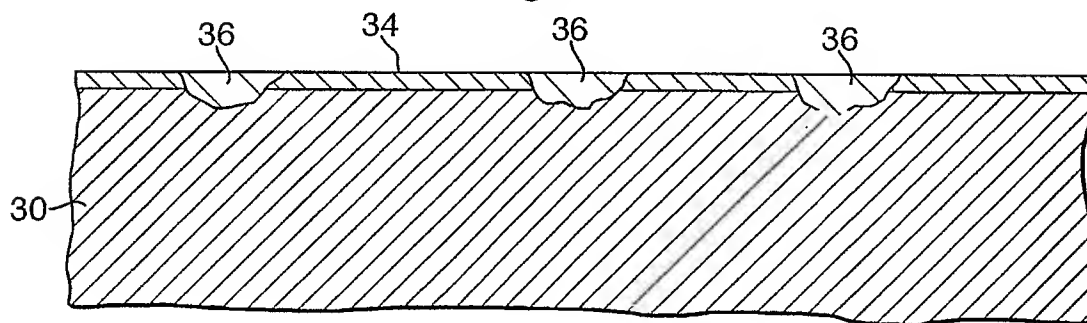
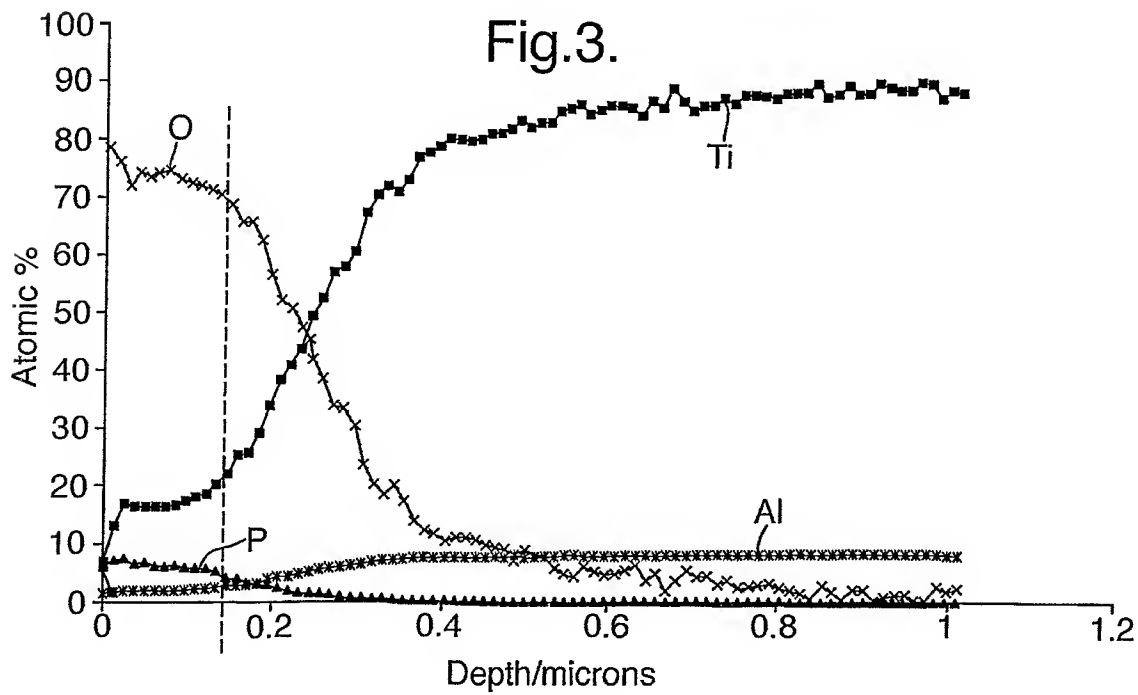


Fig.3.



INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C25D11/26 A61F2/30 A61L27/04 A61L27/06 A61L27/30 A61L27/32 A61L27/54 A61L27/56		
According to International Patent Classification (IPC) or to both national classification and IPC		
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 03/089023 A (ACCENTUS PLC; PICKFORD, MARTIN, EDWARD, LEE; TURNER, ANDREW, DEREK) 30 October 2003 (2003-10-30) cited in the application page 5, line 1 - line 20; claims -----	1-3
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<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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